education

FROM THE JOURNALS Edited highlights of weekly research reviews on https://bit.ly/2PLtil8

Life in the old drug yet

Cisplatin has been around for 50 years. It kills cells by damaging nuclear DNA and is used to treat a wide range of cancers. But it's far from perfect. Resistance and reduced uptake by cancer cells and side effects such as nausea are good reasons to seek an alternative.

The current gold standard treatment for human papillomavirus-positive oropharyngeal squamous cell carcinoma (around 70% of total) is radiotherapy plus cisplatin. This study looked at whether replacement of cisplatin with cetuximab—an antibody against the epidermal growth factor receptor—can preserve high survival and reduce treatment toxicity. The cisplatin group fared better. The estimated five year overall survival was 77·9% in the cetuximab group versus 84·6% in the cisplatin group, with similar levels of toxicity. So, there's life in the old drug yet, and the search for something better goes on.

Lancet doi:10.1016/S0140-6736(18)32779-X

Probiotics for children's tummy bugs

The season of colds and tummy bugs is upon us, and GPs, paediatricians, and emergency medicine doctors are seeing lots of children with gastroenteritis. A prospective, double blind trial enrolled nearly a thousand children aged 3 months to 4 years with acute gastroenteritis who presented to one of 10 US paediatric emergency departments and randomised them to a five day course of the probiotic *Lactobacillus rhamnosus GG*, or to placebo. Just over 10% got worse rather than better over a two week period, but in most, the diarrhoea lasted around two days. Other household members were infected in 10-14% of cases. There was no statistically significant difference between the two groups for any of the measured outcomes. One piece of advice that I will be confident about giving the parents of children with gastroenteritis is—don't bother with probiotics.

N Engl J Med doi:10.1056/NEJMoa1802598

Intensive care for ICU staff

Medicine and nursing are stressful professions, and nowhere more so than in intensive care units (ICUs). The question is whether a five day, multimodal programme, including education, role play, and debriefing could reduce job related stress among ICU nurses? A French study found that it worked well. Job strain (as measured by questionnaires) was only reported by 13% of the intervention group compared with 67% in the control group. Absenteeism over the six month period went down from 8% in the control group to 1%—which seems remarkably low.

I wonder whether it was having five days away from the daily stress of the ICU to reflect and talk to colleagues, as much as the actual content of the course, that made a difference to these nurses.

JAMA doi:10.1001/jama.2018.14284

New hope for peanut allergy

Peanut allergy is becoming more prevalent and is the cause of more allergy related deaths than any other food. A lifetime of vigilance and avoidance are the only solutions at present. Enter AR101—a new peanut derived, oral biologic drug that delivers a specified amount of peanut protein. The name evokes Orwell's sinister Room 101 where prisoners are exposed to their own worst nightmare. I'm not sure whether this is intentional or unfortunate. This well conducted trial found that highly allergic children who were given AR101 could eat higher doses of peanut protein and had a milder allergic reaction during a subsequent challenge, than those who hadn't received AR101. There were no deaths or life threatening adverse events. Study limitations included a narrow demographic (predominantly white males), short follow-up period (the exit challenge was six months after the intervention, so we don't know how long desensitisation lasts), and exclusion of those with severe asthma (who may be most likely to benefit from desensitisation) for safety reasons.

N Engl J Med doi:10.1056/NEJMoa1812856

Aspirin and fish oils to prevent colon cancer

The management of colorectal cancer has improved, but it remains the second most common cause of cancer deaths in the UK. This randomised study asked whether the omega-3 fatty acid eicosapentaenoic acid (EPA) and/or aspirin were better than placebo in preventing sporadic colorectal cancer in a high risk population. Unfortunately, EPA and aspirin didn't reduce the proportion of individuals who had one or more colorectal adenomas, but they both decreased the recurrence of some subtypes of adenoma. The authors say, "the larger effect size of aspirin adds to the weight of evidence for its use in combination with endoscopic screening and surveillance, which provides suboptimal protection against right-sided colorectal cancer."

Lancet doi:10.1016/S0140-6736(18)31775-6

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Disease modifying therapies for multiple sclerosis

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Patricia McGettigan, clinical senior lecturer in clinical pharmacology, Queen Mary's University, London. To suggest a topic, please email us at practice@bmj.com

0.5 HOURS

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A 32 year old woman with multiple sclerosis presented to her general practitioner with a five day history of numbness and weakness in the right leg. She felt well in herself and did not describe any symptoms to suggest an intercurrent infection. She had been taking weekly intramuscular injections of interferon beta-1a for the previous 18 months and reported flu-like symptoms that could last for up to 24 hours after each dose. She asked if there was a need to change her treatment and what alternatives were available.

Multiple sclerosis is a chronic, immune-mediated, demyelinating disorder of the central nervous system.[1] It is a major cause of physical disability in young adults and can have profound implications for cognition, emotional wellbeing, and employment. Patients commonly present with unilateral visual loss (due to optic neuritis), double vision, sensory symptoms, limb weakness, or imbalance.[2] The diagnosis is based on clinical features and findings on magnetic resonance imaging (MRI).[2 3]

Nearly 80-85% of people with multiple sclerosis experience a relapsing course: episodes (attacks or relapses) of new or worsening neurological symptoms lasting at least 24 hours, followed by full or partial recovery, in the absence of fever or infection (fig 1).[3] If left untreated, most people with relapsing multiple sclerosis develop disability over time. This can be caused by incomplete recovery from relapses or due to development of progressive multiple sclerosis, with a steady increase in disability. In 10-15% of people with multiple sclerosis the disease is progressive from the onset (primary progressive multiple sclerosis).

WHAT YOU NEED TO KNOW

- Disease modifying therapies (DMTs) early in the course of active relapsing multiple sclerosis can prevent relapses, new brain and spinal cord lesions, and worsening neurological disability
- Some DMTs are associated with potentially serious adverse reactions, and careful monitoring is required, usually through a specialist multiple sclerosis clinic
- Newer DMTs have better short term outcomes than older DMTs, but there are insufficient data about their long term effectiveness and harms

What treatments are available for multiple sclerosis?

Several oral and monoclonal antibody therapies for multiple sclerosis have become available in the past decade (fig 2).

Relapsing multiple sclerosis—Currently, 15 disease modifying therapies (DMTs) are licensed for relapsing multiple sclerosis, including five preparations of interferon beta and three preparations of glatiramer acetate.[2 4]

Progressive multiple sclerosis—Ocrelizumab,[6] the first treatment for primary progressive multiple sclerosis, has recently been licensed.

Inactive multiple sclerosis—No treatment is advised for patients with inactive multiple sclerosis.[7]

Clinically isolated syndrome—Guidelines recommend interferon beta or glatiramer acetate in patients with a clinically isolated syndrome. This is the first episode of neurological symptoms suggestive of multiple sclerosis with brain MRI abnormalities (indicating a high risk of multiple sclerosis). The aim of treatment is to delay a second attack.[8 9]

The indications differ based on licensing by regulatory agencies (see appendix on bmj.com).

The mechanisms of action of DMTs are not fully understood. Nevertheless, by acting on the immune system that is dysregulated in multiple sclerosis, DMTs limit central nervous system inflammation, preventing the occurrence of relapses and new inflammatory lesions.

How well do they work?

With the exception of ocrelizumab, which is the only drug licensed for primary progressive multiple sclerosis, DMTs have been found to be effective only in the relapsing forms of the disease. There is moderate to high quality evidence from phase III randomised controlled trials and systematic reviews of DMTs.[10 11] These studies show that DMTs reduce relapses, accumulation of new brain MRI lesions, and disability progression over two to three years in active relapsing multiple sclerosis compared with placebo or an active comparator (interferon beta).[4] Based on their impact on relapses compared with placebo (or interferon beta), the DMTs can be categorised as moderately effective (interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod) or highly effective drugs (natalizumab, ocrelizumab, alemtuzumab, cladribine, and mitoxantrone).[7] The highly effective DMTs are associated with more serious safety concerns and require greater safety monitoring.

DMTs generally do not improve established symptoms of multiple sclerosis, though preliminary evidence suggests some improvement in disability with alemtuzumab and natalizumab.[29 30]

MULTIPLE SCLEROSIS OVERVIEW

PRESENTATION

Most typical and common symptoms[2]

- Acute unilateral optic neuritis
- Double vision
- Facial sensory loss/trigeminal neuralgia
- Cerebellar ataxia and nystagmus
- Partial myelopathy
- Sensory symptoms in a CNS pattern
- Lhermitte's symptom
- Asymmetric limb weakness
- Urge incontinence or erectile dysfunction
- Slowly progressive neurologic symptoms (mostly motor)

ATTACK

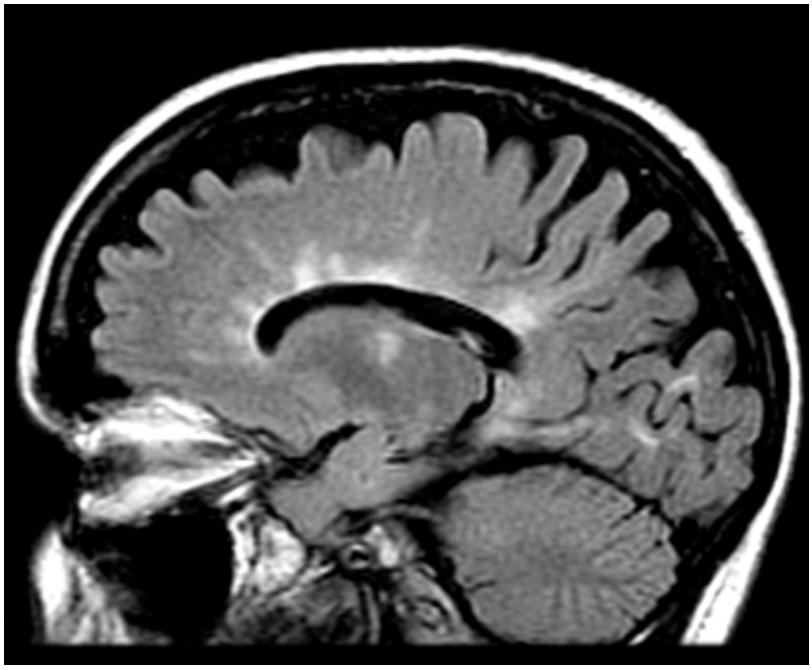
Attack (or relapse)[3]

A monophasic clinical episode with patient-reported symptoms and objective findings typical of multiple sclerosis, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection

		CIS	RELAPSING MS			PROGRESSIVE MS	
PHENOTYPE			Inactive	Active	Highly-active	SPMS (secondary progressive MS)	PPMS (primary progressive MS)
		1st attack suggestive of MS	No clinical attacks and stable MRI	1 relapse in the previous year and/or new T2 or gadolinium-enhancing lesions on MRI	1 relapse and new gadolinium-enhancing lesion(s) and/or significant increase in T2 lesions while on DMTs 2 or more relapses in the previous year and MRI activity in patients not on DMT	Steady increase in neurological disability independent of relapses (disease progression) following an initial relapsing course	Steady increase in neurological disability independent of relapses (disease progression) from disease onset
TREATMENT	DMT[2,4]	– Glatiramer acetate – Interferon beta	Active monitoring with clinical assessment and MRI	– Alemtuzumab – Dimethyl Fumarate – Fingolimod – Glatiramer acetate – Interferon beta – Ocrelizumab – Teriflunomide	– Cladribine – Fingolimod – Natalizumab – Ocrelizumab – Mitoxantrone	No licenced treatments	Ocrelizumab
	STD CARE	Offer high-dose corticosteroids for management of acute disabling relapses after ruling out infections (pseudo-relapse[5]) Offer treatment for ongoing symptoms such as bladder disturbance, constipation, spasticity, and pain Promote brain health including smoking cessation, regular exercise, healthy diet, and weight loss if appropriate Treat comorbidities including depression, hypertension, diabetes, and osteoporosis					

CNS=central nervous system; CIS= clinically isolated syndrome; MS= multiple sclerosis; SPMS= secondary progressive multiple sclerosis; PPMS=primary progressive multiple sclerosis; DMT= disease-modifying therapy; MRI=magnetic resonance imaging; Std=Standard

Fig 1 | An overview of multiple sclerosis with an approach to treatment according to the European Medicines Agency (see also appendix on bmj.com)



LIVING ART ENTERPRISES/SPL

Magnetic resonance imaging of brain (side view) showing characteristic hyperintense lesions (whiter areas) of multiple sclerosis

What are the harms?

Flu-like symptoms (interferon beta); headache (interferon beta, fingolimod); gastrointestinal upset (dimethyl fumarate, teriflunomide); and injection site reactions (interferon beta, glatiramer acetate) are common (≥1% to <10% of patients taking the drug) or very common (≥10% of patients), as reported in the relevant summaries of product characteristics. These reactions are generally mild but can be bad enough that patients stop taking the drug and sometimes require a change of treatment. Infusion reactions are common with alemtuzumab and ocrelizumab.

Observational studies have shown interferon beta and glatiramer acetate are not associated with long term harm; patients can be reassured they are unlikely to experience serious side effects.[34-36]

Oral and monoclonal antibody treatments can have serious adverse reactions (see box 1). Their long term safety profile is unknown. Daclizumab, an anti-CD25 monoclonal antibody, has recently been withdrawn after cases of severe liver injury and immune-mediated encephalitis not observed in phase III clinical trials.

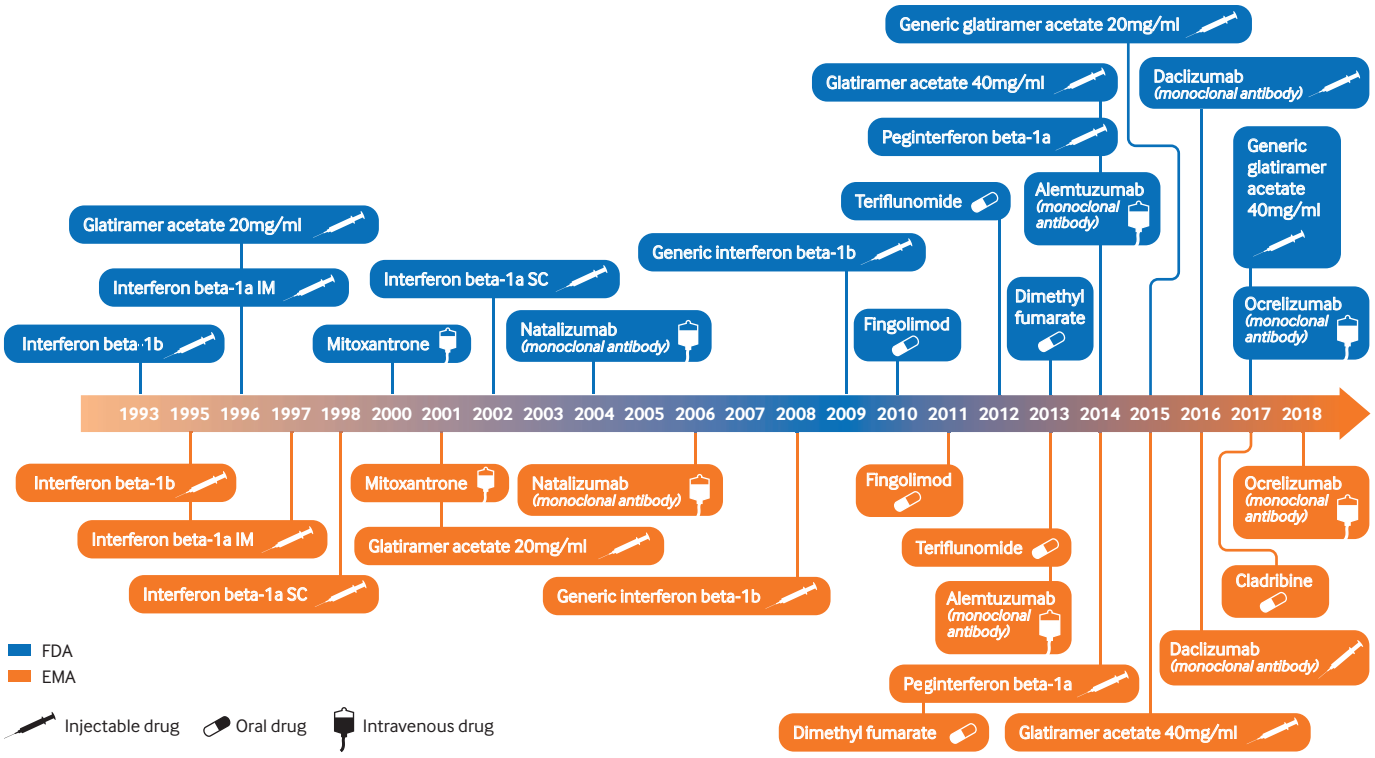


Fig 2 | Timeline of approval of disease modifying therapies (DMTs) for relapsing multiple sclerosis by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Daclizumab was withdrawn in March 2018 because of cases of encephalitis and meningoencephalitis. Glatiramer acetate and mitoxantrone were approved in the EU via national procedures and not initially by the EMA

TIPS FOR SAFER PRESCRIBING

- DMTs are contraindicated in patients with active infections or malignancy, and in patients taking other immunosuppressants[37]
- Fingolimod has interactions with CYP3A4 enzyme inhibitors (azole antifungals, macrolides antibiotics, protease inhibitors) and inducers (rifampicin, carbamazepine, St John's wort), and pharmacodynamic interactions with β blockers and calcium channel blockers. Co-administration of fingolimod with these drugs should be approached with caution and concomitant administration with St John's wort is not recommended.
- Follow regulatory authority guidance on blood, urine, and MRI monitoring requirements.

Pregnancy and breastfeeding

- Women taking DMTs should be counselled to use effective contraception
- DMTs are usually stopped before conception, although interferon beta and glatiramer acetate may be safe during conception and pregnancy.[48] The EMA recently updated the label of branded glatiramer acetate to remove pregnancy as a contraindication
- Teriflunomide is teratogenic, and an accelerated elimination procedure may be required before conception because of its long half-life
- Preconception planning to make decisions regarding DMTs and obstetric care should be considered in women with multiple sclerosis[49]

Vaccinations

- Live or live attenuated vaccines should be avoided in patients taking most DMTs. Patients who are IgG negative for varicella-zoster virus should be immunised, particularly before treatment with fingolimod or cladribine[37]

How are they given and monitored?

DMTs are prescribed and monitored in secondary care, often through specialist multiple sclerosis clinics with neurologists, nurse specialists, and pharmacists. The route (subcutaneous or intramuscular injection, oral, intravenous) and frequency of administration differ by the drug. A discussion of the risks and benefits of treatment is important. Box 2 lists important considerations when selecting DMTs. Blood monitoring is required for all DMTs (except glatiramer acetate), particularly full blood count (to detect lymphopenia) and liver function tests. The frequency and type of blood test and other monitoring, such as brain MRI or urine test, are mandated by regulatory authorities.

Most DMTs require ongoing treatment, with return of disease activity if the drug is interrupted or stopped. Some DMTs (alemtuzumab, cladribine) have immune-reconstitution properties with sustained effects in the absence of ongoing treatment. Adherence to treatment is important, and DMTs may be changed in patients with side effects. There is no guidance on stopping treatment; this is usually decided by the treating neurologist in discussion with the patient based on the response and side effects.

Periodic clinical reviews to check for relapses or disability progression and for MRI are used to monitor response to treatment. Evidence of disease activity on MRI is associated with an increased risk of disability progression even in patients who are clinically stable.[39 40]

Box 1 | Serious adverse reactions with disease modifying therapies for multiple sclerosis and precautions[4 37]

Progressive multifocal leukoencephalopathy (PML)

- This is an opportunistic brain infection, due to reactivation of the John Cunningham virus (JCV), that can complicate treatment with natalizumab and is associated with high rates of death or disability
- JCV serostatus and antibody index should be checked before starting natalizumab (and periodically during treatment) to stratify PML risk
- PML has rarely been reported in patients taking fingolimod (estimated risk ‹1:10 000) and dimethyl fumarate who have not been treated with natalizumab
- MRI monitoring is mandatory in patients treated with natalizumab, fingolimod, dimethyl fumarate, on at least an annual basis, and every 3-6 months in natalizumab-treated patients at high risk of PML[38]

Cardiac arrhythmias

- Fingolimod causes first-dose bradycardia (~1-2%) and rarely transient heart block (‹0.5%)
- An electrocardiogram should be obtained before starting treatment, and the first dose administered with heart rate monitoring for 6 hours after the first dose
- Cases of ventricular tachycardia and sudden cardiac death have also been reported
- Fingolimod should be avoided in patients with a history of ischaemic heart disease or cardiac arrhythmias

Hepatotoxicity

- Deranged liver function tests commonly occur with several DMTs (particularly interferon beta, dimethyl fumarate, and fingolimod)
- Individual cases of fatal liver injury have been reported with leflunomide (the pro-drug of teriflunomide). Teriflunomide should be avoided in people with a history of liver disease

Secondary autoimmunity

- Autoimmune thyroid disease, immune thrombocytopenic purpura, and glomerulonephritis may occur in people treated with alemtuzumab, most often in the second or third year after starting treatment (risk of secondary autoimmunity ~50% at 5 years)

Malignancy

- DMTs should not be prescribed in patients with an active malignancy, and their safety in patients with a history of cancer is uncertain
- Fingolimod is associated with an increased risk of skin cancers, particularly basal cell carcinoma
- Mitoxantrone is associated with an increased risk of acute myeloid leukaemia (0.5-1%) and possibly solid-organ cancers
- The long term risk of cancer with other DMTs is unknown

Box 2 | Factors influencing choices of DMT for multiple sclerosis

Disease factors

- Disease course
- Relapse rate
- Relapse severity
- MRI findings

Patient factors

- Patient preferences
- Desire for pregnancy
- Comorbidities
- Burden of monitoring
- Drug tolerability

Healthcare system factors

- Drug availability
- Drug licencing
- Drug costs
- Resources (such as infusion facilities)

How cost effective are they?

DMTs account for over half of direct medical costs in people with multiple sclerosis.[44] Several studies have found that DMTs are not cost effective at accepted economic thresholds.[44] Of the currently available DMTs, alemtuzumab may be most cost effective because of higher efficacy and unique dosing strategy (two cycles of treatment over two years with further treatment given only if needed).[11]

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: WJB has received speaker fees for educational activities from Merck Serono, which produces interferon beta-1a used to treat multiple sclerosis.

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EDUCATION INTO PRACTICE

- How might non-specialists be involved in discussions about treatments for multiple sclerosis?
- If you provide care for women who take DMTs have you or another clinician discussed contraceptive options?
- Would placing an alert on the electronic patient record for people receiving DMTs aid recognition of complications of treatment in patients presenting acutely in primary or secondary care?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We asked two patients who attend our specialist multiple sclerosis clinic to comment on the draft manuscript. They highlighted the importance of early referral to a specialist multiple sclerosis team, the importance of lifestyle factors and burden of monitoring when selecting DMTs, and contraception and preconception counselling in women with multiple sclerosis.

10-MINUTE CONSULTATION

HIV post-exposure prophylaxis (PEP)

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CPD READING
0.5 HOURS

LEARNING MODULE
See http://learning.bmj.com for linked learning module

A 22 year old man presented to the emergency department for HIV post-exposure prophylaxis (PEP). Twenty six hours previously, he had anal receptive intercourse without a condom with a man of unknown HIV serostatus. He had immediate testing for HIV (using a fourth generation antibody/antigen assay as recommended[1 2]), hepatitis B and C serologies, syphilis serology, and urine nucleic acid amplification tests for gonorrhoea and chlamydia. In the emergency department he received a three day supply of combined emtricitabine/tenofovir disoproxil fumarate (TDF/FTC) (one tablet daily) plus raltegravir (400 mg twice daily). He was referred to be seen urgently in the next three days in an outpatient clinic for continuing management.

PEP is a safe and effective HIV prevention modality for people with a recent (within 72 hours) exposure to HIV. People with HIV exposure often present to primary care clinics and emergency departments, so it is useful for non-specialists to have confidence in prescribing PEP. Clinicians caring for people presenting with a recent HIV exposure require knowledge of recommended diagnostic testing after sexual exposure and blood borne exposure, PEP regimens, schedule of short and long term follow-up, and the potential for physical and psychological trauma (eg, in the case of sexual assault). This article offers practical advice and resources for clinicians caring for individuals who present for care after an actual or potential exposure to HIV that is non-occupational.

WHAT YOU NEED TO KNOW

- HIV post-exposure prophylaxis (PEP) is a safe and effective treatment strategy aimed at preventing infection in those with a recent HIV exposure
- PEP is typically prescribed as three HIV antiretroviral drugs started within 72 hours after exposure, and continued for 28 days
- PEP is most useful for people with a single exposure or infrequent moderate-to-high risk exposures to HIV. Pre-exposure prophylaxis may be better suited to those with ongoing risk

What you should cover

The risk of the exposure

Ask your patient for details of the exposure, including the precise time and the nature of the exposure. The table shows estimates of the risk of HIV by type of exposure. Ask the patient if they are aware of having a history of sexually transmitted infections or viral hepatitis to assess their baseline risk. If the HIV exposure was through sexual activity, ask if the person is aware if this sexual partner (the "source patient") has any sexually transmitted infections. Take a history of other recent potential exposures and of previous use of PEP.

HIV and other communicable disease risks of the source patient

If the medical history of the source is unknown, ask if there is an opportunity to contact the source for diagnostic testing (eg, for HIV, hepatitis B and C). There are often considerable challenges in confirming the source patient's HIV serostatus; however, establishing this history can meaningfully facilitate decisions about the need (or not) for PEP.

Sources who are known to be HIV positive but have a recently documented undetectable viral load (<200 copies/mL for more than six months) have a zero to negligible risk for sexual HIV transmission[3] and PEP is unlikely to provide benefit. PEP may be considered in these situations if the source has questionable adherence to his or her antiretroviral medications, has a known detectable viral load, or if the timing of the most recent undetectable viral load cannot be established.

Balancing the risks and benefit of PEP

PEP is typically initiated when the exposure risk is moderate to high[4] (table) and when the source has a

EDUCATION INTO PRACTICE

- Do you have PEP starter packs at work? If not, what is the local pathway for rapid access to PEP?
- How might you address the high rate of attrition between initiating PEP and attending follow-up appointments?
- Can you identify local data sources of HIV prevalence in your population that might help you assess risk of a source patient?

Estimated risk of acquiring HIV from an infected source by type of exposure*

Exposure type	Rate for acquisition of HIV per 10 000 exposures
Needle sharing during injection of drugs	63
Percutaneous (needlestick)	23
Receptive anal intercourse	138
Receptive penile-vaginal intercourse	8
Insertive anal intercourse	11
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	Low
Insertive oral intercourse	Low

*From the US guidelines for antiretroviral post-exposure prophylaxis after sexual and injection drug use exposure to HIV[2]

non-negligible risk of HIV,[1-6] such as with condomless anal insertive or receptive intercourse or sharing of drug injecting paraphernalia.[3-6] When adherence or recent viral load data are unknown, PEP is frequently offered and subsequently discontinued during follow-up if additional data reveal the source to be non-infectious. Share with the patient the uncertainty around risk of acquisition from both the source and the exposure type. This facilitates a decision that takes into account the patient's preferences and perception of risk.

Psychological, social, and safeguarding concerns

The presentation of a patient for PEP after a confirmed or potential HIV exposure is seen as an important opportunity for health promotion and screening for abuse. Take a careful history to explore the possibility of sexual assault, ongoing risk exposure, and/or misuse of alcohol or drugs. Ensure that the patient has access to primary healthcare services and social services, as necessary.

What you should do

Prescribing PEP

PEP regimens typically comprise three antiretroviral drugs that are started within 72 hours after a potential or confirmed HIV exposure and continued for 28 days.[1-6] Common PEP drug regimens include a combination tablet of tenofovir disoproxil fumarate plus emtricitabine (TDF/FTC 300mg/200mg once daily) and an integrase inhibitor such as raltegravir (400 mg twice daily). Until recently, dolutegravir (50 mg daily) was commonly used as a PEP regimen with TDF/FTC. However, recent data relating its use to neural tube defects.[7] have led the World Health Organization, European Medicines Agency, and the US Food and Drug Administration to recommend against using it in women of child bearing age who are not on effective contraceptive therapy. Consequently, raltegravir should be recommended in most cases of PEP in women. Health centres that see patients presenting for PEP that do not provide primary or chronic HIV care (eg, urgent care, walk-in and emergency health providers) can prepare PEP "starter packs" with a three day supply of preferred PEP drugs, to bridge presenting patients to longer term care providers.

Where integrase inhibitors are not readily available, a boosted protease inhibitor based regimen is recommended in addition to combination TDF/FTC, with careful consideration of potential drug interactions between any active medicines the patient is taking and the boosted protease inhibitor. Finally, a combination of zidovudine and lamivudine is typically recommended in place of TDF/FTC in individuals with substantial renal insufficiency (creatinine clearance <60 mL/minute). Infectious disease consultation is recommended where the source is known to have HIV drug resistance or if the patient is on therapy for concomitant tuberculosis.

Data from clinical trials and rigorous observational studies in humans are lacking. However, decades of observational experience with PEP[8 9] have shown it to be associated with a substantial reduction in the risk of HIV acquisition after percutaneous needle exposure and condomless sex. Indeed, most PEP "failures" reported in the literature are confounded by ongoing risk or sub-optimal PEP adherence.[10 11] Animal studies support this protective effect, particularly when PEP is initiated within 72 hours of exposure.[12 13]

Most patients tolerate PEP without any issues, although nausea, diarrhoea, and headaches may be reported. These frequently resolve within the first 48 hours of initiating PEP. Raltegravir is associated with a small risk[14] of rhabdomyolysis: inform patients about the risk and advise them to let their clinician know if they experience myalgia and to avoid statins while taking raltegravir. Advise patients to take the medication at roughly the same time of day, and that drug adherence is important to ensure maximum efficacy.

HOW THIS ARTICLE WAS CREATED

This article was created by reviewing major national and international HIV prevention guidelines, including those of the UK, USA, Canada, and World Health Organization.[1-5] Additionally, other sentinel HIV prevention studies were included that relate to risk of HIV transmission,[3 4] adherence, and follow-up issues.[15]

RECOMMENDED RESOURCES

- Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis[1]
- US guidelines for antiretroviral postexposure prophylaxis[2]
- British HIV Association guidelines for the use of post-exposure prophylaxis after sexual exposure[5]
- WHO guidelines on post-exposure prophylaxis for HIV[6]

JUSTIN SULLIVAN/GETTY IMAGES

Baseline testing, screening for sexually transmitted infection, and prevention of onward transmission

Major national and international guidelines on HIV prevention differ in recommended investigations and follow-up schedules. In general, initial investigations include a complete blood count, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin to establish baseline values and also to potentially help choose a PEP regimen as certain components (eg, TDF) are renally metabolised.

Baseline testing for other infectious diseases includes serologic screening for HIV with preference for use of a point of care HIV test, if available. Testing should also be performed for chlamydia, gonorrhoea (urine nucleic acid amplification test; rectal and pharyngeal culture or nucleic acid amplification tests, as indicated by exposure), syphilis serology, and hepatitis C serology, immunity to hepatitis A (hepatitis A IgG), immunity or infection with hepatitis B (surface antibody, surface antigen, core-total antibody). Perform a pregnancy screen where appropriate.

Empiric treatment for sexually transmitted infections (STIs) is typically provided to patients who have experienced sexual assault and occasionally to others in whom risk is high.[1-5] STI treatment should adhere to local guidelines. Advise patients to use barrier protection during sex until at least their four month follow-up HIV screen is confirmed as negative and to avoid sharing drug injecting paraphernalia. Ongoing health promotion strategies in clinic include counselling on safe sex, advice on safer injecting practices, vaccination for hepatitis A and/or hepatitis B viruses if serology results indicate they are appropriate, and referral to appropriate resources for those with a history of abuse, mental health comorbidities, and drug or alcohol misuse.

Follow-up care

After transitioning from a PEP starter pack to the full 28 days of treatment, patients are typically seen again after two weeks in primary care or HIV clinic, where they are evaluated for medication toxicity and adherence. They should be seen again 4-6 weeks after PEP initiation to repeat screening for HIV and STI, and for pregnancy testing if relevant. Attrition rates between the emergency department and clinics are high,[15] and psychosocial and logistic support should be considered at every point of contact with the patient to facilitate follow-up. We find it useful for patients to identify and designate a friend or relative at the first point of contact to help ensure the patient follows up in clinic and to assist with drug adherence. We also find it helpful to confirm a patient contact information, and we will repeatedly attempt to contact patients should they miss an appointment to facilitate timely follow-up and completion of the recommended course of therapy and follow-up testing schedule.

HIV testing is repeated four months after the inciting exposure to confirm transmission did not occur at the time of exposure. Perform an additional HIV screen at six months if hepatitis C was acquired from the inciting exposure, as acute hepatitis C infection may delay HIV seroconversion.[1-5]

PEP may be discontinued early if there is evidence of a negative HIV test or confirmation of a recent undetectable HIV-1 RNA viral load in the source patient (and there is no suspicion that the source has acute HIV infection). Patients with ongoing risk factors for HIV acquisition should be considered for HIV pre-exposure prophylaxis. If seroconversion occurs, refer patients to an HIV treatment provider for immediate initiation of antiretroviral therapy.[16 17]

Competing Interest: All authors have completed the ICMJE uniform disclosure form atwww.icmje.org/coi_disclosure.pdfand declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Two patients were consulted and contributed to the creation of this article. Both initiated PEP following a sexual exposure, and one patient ultimately transitioned to pre-exposure prophylaxis care. Both patients had targeted suggestions for abuse screening (eg, drugs, alcohol, sexual) and stressed the importance of connecting patients with appropriate psychosocial support when necessary.

CASE REVIEW

Acute enlargement of a vascular plaque and gait changes in a young girl

A 15 month old girl presented to the emergency department with a one week history of unsteady gait and approximately three to four unexplained falls each day. She had been walking independently and without difficulty since she was 12 months old. At birth, she had a broad pink patch on the right medial buttock, which had been diagnosed on clinical examination as a congenital haemangioma. The site had grown proportionally with the patient until these symptoms started, when this vascular stain became acutely indurated, and a contiguous, erythematous plaque appeared superiorly, overlying the sacrum. On examination, a swollen, violaceous, warm, subcutaneous plaque with superimposed telangiectases was noted overlaying the sacrum. This extended to the right buttock, where an accompanying pink-purple stain was present (figure). No thrills or pulsations were noted. Neurological examination showed no paralysis. Relevant laboratory findings are shown in the table.

1 **What are the differential diagnoses of lumbosacral swelling in children?**

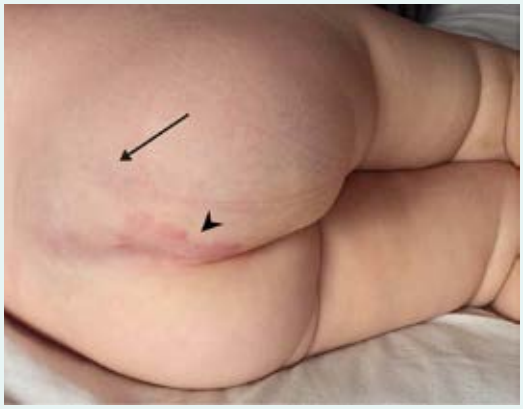
2 **What is the most likely diagnosis?**

3 **How would you manage this patient?**

Submitted by Kathleen T Tedesco, Jay Sarthy, Navin Pinto, and Markus D Boos

Parental consent obtained.

Cite this as: *BMJ* 2018;363:k4679



A swollen, violaceous, subcutaneous plaque overlaying the sacrum with subtle overlaying telangiectases (arrow), extending contiguously to the right buttock with a more prominent vascular stain (arrowhead)

Relevant investigation findings

Test	Result	Reference range
Full blood count (mL)	156 000	250 000-600 000
Fibrinogen (mg/dL)	142	230-450
D-dimer (µg/mL)	2.0	≤0.5
Beta-hCG (mIU/mL)	2	0-5
Serum α fetoprotein (ng/mL)	54 700	0-12
Ultrasound	Hypervascular mass consistent with a congenital haemangioma	NA
Magnetic resonance imaging (MRI) spine and pelvis	Cystic/solid sacrococcygeal mass with metastases to the T12 vertebral body, causing cord compression	NA
Computed tomography of the thorax, abdomen, and pelvis	No disseminated disease	NA

answers

For extra material, including patient outcome, go to bmj.com/endgames

CASE REVIEW

Acute enlargement of a vascular plaque and gait changes in a young girl

1 The differential diagnoses for paediatric lumbosacral swelling include congenital haemangioma, deep infantile haemangioma, kaposiform haemangioendothelioma (KHE), sacral meningocele, lipoma, dermatofibrosarcoma protuberans, sacrococcygeal teratoma (SCT), rectal abscess, and cellulitis. KHE and non-accidental trauma should also be considered when a child presents with an acutely swollen, red-blue mass.

2 The patient's clinical appearance, presence of a sacrococcygeal mass with metastases on MRI imaging, and an elevated serum α fetoprotein support the diagnosis of malignant SCT. The gait abnormalities were likely caused by the cord compression noted on MRI evaluation. Some SCTs have overlying vascular staining and are easily misdiagnosed as a vascular anomaly.[1]

3 Early and complete surgical resection of SCT is the mainstay of successful treatment for presacral germ cell tumours. Cisplatin based chemotherapy improves overall survival rates to approximately 80%.

After treatment, assess for disease recurrence with imaging, serial monitoring of α fetoprotein levels, and physical examination every 3-6 months for five years.

LEARNING POINTS

- Include SCT in the differential diagnosis of congenital and infantile growths and vascular anomalies of the lumbosacral region, as early and prompt recognition can limit associated morbidity and mortality
- SCTs are the most common germ cell tumours in neonates and infants
- Many SCTs are asymptomatic but there may be renal or bowel dysfunction and neurological changes.

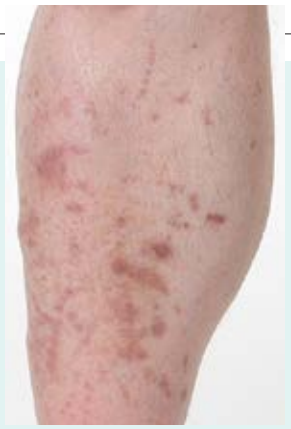
CPD READING
0.5 HOURS

You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.

LEARNING MODULE

Articles with a "learning module" logo have a linked BMJ Learning module at http://learning.bmj.com.

Diabetic dermopathy



A 48 year old man with type 2 diabetes presented with a two year history of asymptomatic spots on his shins (figure). Examination showed multiple pretibial patches which were irregularly shaped, pigmented, and atrophic. A few similar lesions were seen on his forearms.

This is diabetic dermopathy (sometimes called shin spots). It is seen in 17-40% of people with diabetes mellitus type 1 and 2. The condition can sometimes also be seen on the forearms. It is associated with increased age and longer duration of diabetes and is believed to have a microangiopathic origin. It often occurs with other diabetic complications, like retinopathy and peripheral neuropathy. Differential diagnoses include necrobiosis lipoidica, post-inflammatory hyperpigmentation, hemosiderin pigmentation, and skin staining after antimalarials and quinolones.

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Patient consent obtained

Cite this as: *BMJ* 2018;363:k4882

If you would like to write a Minerva picture case, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx

Reducing salt

Many guidelines recommend reduction of dietary salt intake for people with heart failure, but according to a systematic review, there's not much evidence to support this advice. The reviewers identified nine relevant studies, none of which had more than 100 participants (*JAMA Intern Med*). Only two of the seven trials in outpatients with chronic heart failure reported clinical improvement when salt intake was reduced. Indications that restriction of salt intake was beneficial for inpatients with acute heart failure were even weaker.

Ramadan

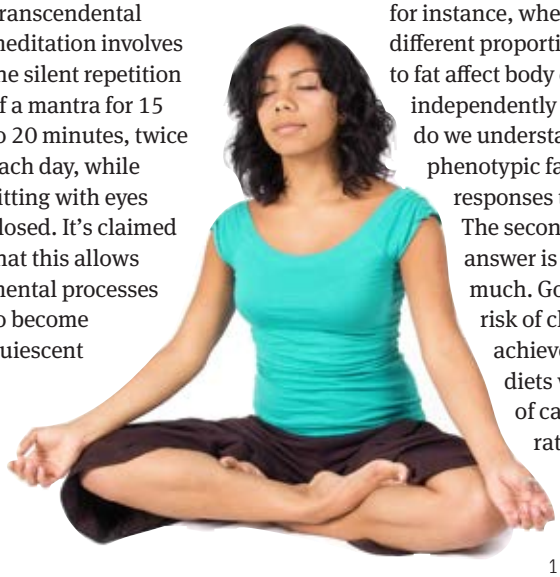
Ramadan is the ninth month of the Islamic calendar, and during this time Muslims fast from dawn to sunset. A study from Burkina Faso suggests that this has consequences for the fetus if a pregnant woman observes Ramadan in the earlier part of gestation. Mortality in children under 5 born to Muslim mothers was 20-30% higher than in those born to non-Muslim mothers if Ramadan had occurred at the time of conception or in the first two trimesters. Having a Muslim mother had no association with child mortality when there had been no fetal exposure to Ramadan (*Am J Epidemiol*).

Venoplasty in multiple sclerosis

Multiple sclerosis attracts its fair share of wacky theories and sometimes they prove hard to refute. One example is the idea that the disease results from chronic cerebrospinal venous insufficiency due to anomalies of the internal jugular and azygos veins. Several uncontrolled studies reported that venous angioplasty was beneficial. However, evaluated in a randomised double blinded trial, venoplasty turned out to be no better than sham intervention for both clinical and magnetic resonance imaging outcomes (*Neurology*). This is the second randomised controlled trial that has failed to find improvements after venous angioplasty. Minerva hopes that no more will be needed.

Transcendental meditation

Transcendental meditation involves the silent repetition of a mantra for 15 to 20 minutes, twice each day, while sitting with eyes closed. It's claimed that this allows mental processes to become quiescent and produces a state of restful alertness. Ten years ago, a Cochrane review concluded that there wasn't enough evidence to judge its effectiveness in anxiety disorders, but a recent randomised controlled trial shows that it may be helpful for people with post-traumatic stress disorder (*Cochrane Database Syst Rev*). Among 200 people with a diagnosis of post-traumatic stress disorder following active military service, those taught how to meditate experienced a greater reduction in symptoms than those treated with exposure therapy or health education (*Lancet*).



Fats and carbohydrates

What's the optimal ratio of carbohydrate to fat in the diet to prevent chronic disease and obesity? A review in *Science* comes up with two answers. The first is that more research is needed. We don't know, for instance, whether diets with different proportions of carbohydrate to fat affect body composition independently of body weight. Nor do we understand the genetic and phenotypic factors that modify responses to different diets. The second, more pragmatic answer is that it may not matter much. Good health and low risk of chronic disease can be achieved for most people on diets with a broad range of carbohydrate to fat ratios (*Science*).

Cite this as: *BMJ* 2018;363:k4924